Bioresearch Monitoring

Notice of Disqualification

FDA Inspection Reveals Clinical Investigator Submitted False Data

On October 24, 2003, FDA's New Orleans District Office received notification from FDA's Center for Drug Evaluation and Research (CDER) that a "Notice of Disqualification to Receive Investigational New Drugs (IND)" was issued to Dr. Chavaramplakil P. Mathew, New Orleans, Louisiana. A June 2000 inspection by the New Orleans District Office of Dr. Mathew's drug clinical trials revealed significant violations of the regulations, including: submitting false data to the study sponsor; failing to conduct studies in accordance with the investigational plans; failing to maintain adequate and accurate case histories on each individual participating in the studies; and, failing to personally conduct or supervise the clinical investigations.

The Notice, signed by Dr. McClellan on September 24, 2003, advised that Dr. Mathew could no longer receive INDs for study. In June 2002, Dr. Mathew informed FDA that he did not wish to have a hearing to determine whether he could remain entitled to receive INDs.

Counterfeit Drugs

FDA and the U.S. Attorney for the Western District of Texas Announce Guilty Plea in Drug Counterfeiting Case

FDA and the U.S. Attorney for the Western District of Texas announced that Hadi M. Ghandour, owner of Genapharm, Inc. of Austin, Texas, pleaded guilty on March 9, 2004 to 4 counts of an indictment charging conspiracy to introduce misbranded and unapproved new drugs into interstate commerce, counterfeiting human growth hormone, and possessing controlled drugs with intent to distribute.

Through his plea Ghandour admitted engaging in a conspiracy to sell unapproved, misbranded, counterfeit and Schedule I controlled drugs from 1999 to 2001. Ghandour sold these drugs through businesses he controlled and represented as wholesalers of dietary sports supplements. Ghandour also sold drugs directly to consumers, such as body builders, and through other channels. The drugs included are:

- Tiratricol, tri-iodothyroacetic acid (TRIAC), a potent thyroid hormone;

- 1,4 Butanediol, which converts into gamma hydroxybutyric acid (GHB), a Schedule I Controlled Substance, when metabolized by the human body;

- Counterfeit Nutropin AQ (Somatropin), HGH, or recombinant human growth hormone, manufactured by Genentech, Inc. for children with growth hormone deficiency;

- 4 Bromo-2, 5-dimethoxyphenethylamine (2CB or Nexus), a Schedule I Controlled Substance; and,

- BZP, if combined with 1-(3-trifluoromethylphenyl) piperazine (TFMPP) has stimulant and hallucinogenic effects similar to ecstasy, a Schedule I Controlled Substance.

Hadi Ghandour faces up to 5 years in prison and a fine of $250,000 on each count. It should be noted that Ghandour was previously convicted in 1998 of counterfeiting drug labels.

Two other persons involved in these offenses, Derek Ettinger and Joel Desmarais, were previously convicted and sentenced. Derek Ettinger was sentenced on May 15, 2003 to 30 months in a Federal Correctional Institution followed by 3 years of supervised release for his role in counterfeiting human growth hormone and possession with intent to distribute controlled substances. Joel Desmarais was sentenced on May 30, 2003 to 36 months supervised release for introducing an unapproved new drug into interstate commerce and aiding and abetting.

The investigation was conducted by Special Agents of FDA's Office of Criminal Investigations (OCI) and the Drug Enforcement Administration (DEA), with assistance from FDA's Dallas District Office and the Texas Department of Health. The prosecution was handled by Assistant U.S. Attorney's Michelle McElroy and Elizabeth Cottingham and FDA's Attorney Laura Pawloski, who acted as a Special Assistant to the U.S. Attorney.

Good Manufacturing Practices

Contract Drug Testing Laboratories

FDA Inspection Leads to Warning Letter

Analytical Laboratory Found Not Following SOPs

On October 22, 2003, FDA's New Orleans District Office issued a Warning Letter to Tri-State Analytical Laboratory LLC, Johnson City, Tennessee, as the result of an inspection on July 23 - 25, 2003, which found deviations from the Current Good Manufacturing Practice (CGMP) regulations. The deviations found at this contract drug testing laboratory included test reports sent to clients stating that a sample met specifications when out-of-specification results had been found, validations were not performed according to the firm's validation Standard Operating Procedures (SOP), and reference standards and reagents were used past their validation period.

Manufacturers of Finished Pharmaceuticals

Warning Letter Cites Serious CGMP Problems

On June 15, 2004, FDA's Dallas District Office issued a Warning Letter to Ms. Darlene M. Ryan, President, Pharma Fab, Grand Prairie, Texas. FDA inspected this pharmaceutical manufacturing facility from January 5 - 14, 2004. FDA investigators documented serious deviations from CGMP regulations.

This inspection revealed Pharma Fab's quality, production, facilities and equipment, and materials systems employed during the manufacturing, processing, packing and holding of the firm's cough and cold prescription drug products did not conform to CGMPs. Therefore, these drug products are adulterated under the Federal Food, Drug and Cosmetic Act.

The following are examples of the significant deficiencies regarding Pharma Fab operating systems:

- Failure of the Quality Control Unit to review and approve drug product production and control records to determine compliance with all established approved written procedures before a batch is released or distributed;

- Failure to investigate the failure of a batch or any of its components to meet any of its specifications;

- Failure to follow written production and process control procedures in the execution and documentation of production and process control functions at the time of performance;

- Failure to establish and follow written procedures prescribing a system for reprocessing batches that do not conform to standards or specification, and the steps to be taken to insure that the reprocessed batches will conform with all established standards, specifications, and characteristics;

- Failure to establish a written testing program designed to assess the stability characteristics of drug products. For example, Pharma Fab did not have a uniform rationale to determine which liquid pharmaceutical products would be tested for microbiological determinations and preservative effectiveness. Any liquid formulation that contains a preservative system to control against bacteria or fungi growth must be evaluated for its intended preservative effectiveness;

- Failure to review complaints as part of an annual product review in order to evaluate the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures; and,

- Failure to clean, maintain and sanitize equipment and utensils at appropriate intervals to prevent malfunctions and contamination that would alter the safety, identity, strength, quality or purity of the drug product.

The Warning Letter noted that FDA was in receipt of Pharma Fab's written responses dated February 5 and 13, 2004, and March 3, 2004. The Warning Letter acknowledged that the corrective actions Pharma Fab listed in their response addressed some of the specific concerns.

Warning Letter Issued for Serious CGMP Violations

On September 15, 2004, FDA's New Jersey District Office issued a Warning Letter to Dr. Arvind Dhruv, President and CEO, Guardian Drug Company, Inc., Dayton, New Jersey. An FDA inspection of this manufacturing facility in Dayton,

New Jersey, was conducted from February 24 - April 23, 2004. During the inspection, an FDA investigator documented numerous deviations from the CGMP regulations. These deviations caused these drug products to be adulterated under Section 501(a)(2)(B) of the Act.

The deviations observed during the inspection included the following:

- Failure to follow the procedures applicable to the quality control unit;

- Failure to establish adequate written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess;

- Failure to assure that test procedures are scientifically sound;

- Failure to assure that investigations are performed and documented when unexplained discrepancies have occurred. For example:

  There was no investigation of black particulates found in simethicone fluid raw material, nor were any of the other simethicone products reviewed to determine if other simethicone raw material obtained from the same vendor were similarly contaminated; and,

  Gastro Bismuth Liquid was returned by a customer due to product separation; however, no investigation was conducted to determine the cause of the product separation when this did not appear to be a normal occurrence.

- Failure to reject drug products failing to meet established standards or specifications and any other relevant quality control criteria. For example:

  During in-process and release testing of Senna-Lax Tablets, lot 159-6319, the quality control unit failed to observe that the tablets did not meet specification, in that the "GDC" imprint on the lower side of the tablets was missing. In fact, the analyst recorded that the product was properly

imprinted. This lot was released and distributed.

- Failure to establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity;

- Failure to have and follow an adequate written stability program designed to assess the stability characteristics of the drug products;

- Failure to clean equipment to prevent contamination that would alter the safety, identity, strength, quality, or purity of drug product beyond the official or other established requirement; and,

- Failure to have and follow a written procedure that describes the preparation of master production and control records that include complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.

The Warning Letter acknowledged the firm's response dated May 27, 2004, but noted that the response did not provide sufficient evidence that the deviations had been or would be satisfactorily corrected so that the firm could attain substantial compliance on a long-term basis.

Warning Letter Issued for Eye Drops

Adulteration and Misbranding Violations Result in Warning Letter

On August 18, 2004, FDA's New Orleans District Office issued a Warning Letter to Victor J. Santos, President, Natureplex, LLC, Memphis, Tennessee. During an inspection of Natureplex, LLC on February 23 - 26, 2004, FDA investigators documented numerous violations of the CGMP regulations.

These violations caused the firm's drug products to be adulterated under Section 501(a)(2)(B) of the Act. In addition, the ophthalmic drug products, Eye Drops Allergy Relief, Eye Drops Artificial Tears, and Eye Drops Extra Relief, are misbranded under Section 502(a) of the Act. The violations included, but were not limited to the following:

Adulteration:

- Failure to establish and follow written procedures designed to prevent microbiological contamination of drug products purporting to be sterile;

- Failure to clean and sterilize drug product containers and closures to assure they are suitable for their intended use;

- Failure to conduct appropriate laboratory test on each batch purporting to be sterile;
- Failure to test in-process materials for identity, strength, quality, and purity as appropriate and to approve or reject in-process materials by the quality control unit;

- Failure to have adequate batch production and control records;

- Failure to have adequate written procedures for production and process controls designed to assure drug products have the identity, strength, quality, and purity they purport to possess;

- Failure to establish adequate written procedures for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product; and,

- Failure to assure each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform the assigned function.

Misbranding:

The Warning Letter advised that Eye Drops Allergy Relief, Eye Drops Artificial Tears, and Eye Drops Extra Relief ophthalmic drug products are misbranded, because they each failed to bear a tamper-evident packaging labeling statement.

Eye Drops Allergy Relief and Eye Drops Artificial Tears ophthalmic drug products also bore the warning statement “Ask a doctor before use if you have narrow angle glaucoma.” The ingredients present in Eye Drops Allergy Relief and Eye Drops Artificial Tears do not require a warning regarding narrow angle glaucoma. The

Warning Letter noted that use of that warning on the product labels is misleading, and misbrands the products.

Warning Letter Issued to Pharmaceutical Firm

Firm Fails to Investigate Failure of Drug Products to Meet Established Drug Specifications

On June 23, 2004, FDA's Kansas District Office issued a Warning Letter to Roxianne G. Downing, CEO/Chairman, Qualis, Inc., Des Moines, Iowa. Between March 22 and April 2, 2004, an FDA investigator performed an inspection of the Qualis' pharmaceutical manufacturing, Des Moines, Iowa. This inspection revealed serious deviations from CGMP regulations. These deviations caused Qualis' drug products to be adulterated under Section 501(a)(2)(B) of the Act.

Deviations observed during the establishment inspection included, but are not limited to the following:

- Failure to follow written procedures applicable to the function of the quality control unit;

- Failure to thoroughly investigate failures of finished drug products or drug product components to meet established specifications. For example, there was no investigation to determine the reason for part of a lot becoming unusable in storage or of the impact of the use of the remaining material in drug products. In addition, there was no investigation or follow-up to determine the cause for low menthol assays, both upon initial testing and after reworking the product, in a lot of Therapeutic Pain Relieving Gel;

- Written procedures for production and process control were inadequate to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess;

Components were not handled and stored in a manner to prevent contamination. Examples included:

a. A lot of Trisodium Phosphate was found opened while sitting on a cart with other raw materials, which were going to be used in manufacturing product on the following day; and,

b. A box of product was found opened while sitting on a shelf in the raw materials storage area. This box had dried moisture stains with white, recrystallized salts on several areas of the box.

- Failure to perform operations within separate or defined areas or to use other control systems as are necessary to prevent contamination or mix-ups;

- Failure to establish adequate acceptance criteria for sampling and testing to assure that batches of drug products meet each appropriate specification; and,

- Failure to record the execution of production and process control functions at the time of performance.

Pharmakon Laboratory Enjoined for CGMP Violations

U.S. v. Pharmakon Laboratory, Inc. (M.D. Fla.). On October 3, 2003, Judge Richard A. Lazarra entered an Order granting in part and denying in part the government's

motion for preliminary injunction against Pharmakon Laboratory, Inc. (Pharmakon), a manufacturer of prescription and over-the-counter (OTC) drugs. The Complaint for Injunction alleged that Pharmakon introduced adulterated drugs into interstate commerce and caused the adulteration of drugs. The drugs are adulterated in that they were not manufactured in compliance with CGMPs.

The Order stated that Pharmakon is enjoined from violating the Act, and required Pharmakon's consultant to conduct a monthly audit of the firm and submit his findings within seven days to the Court and FDA until further Order. In addition, the Order prohibits Pharmakon from severing its relationship with its consultant without prior approval of the Court. The Court retains jurisdiction over the matter and reaffirms FDA's right to inspect Pharmakon in accordance with the law.

On September 14, 2004, the government filed a Motion for Leave to Amend the Complaint to include misbranding and unapproved new drug charges. On September 22, 2004, the Court granted the government's motion, and the Amended Complaint for Injunction was filed on October 29, 2004.

Repackers of Pharmaceutical Products

Warning Letter Issued to Repacker

FDA Inspection Reveals Problems with Possible Cross-Contamination

On February 27, 2004, FDA's San Francisco District Office issued a Warning Letter to Mark A. Horne, President, PharmPak, Inc., San Rafael, California. During

an inspection of PharmPak, Inc., on August 25 - September 3, 2003, FDA investigators determined that PharmPak, Inc. repacks various drug products, which are human drugs under the Act.

The inspection revealed that the drugs repacked by PharmPak, Inc. were adulterated under the Act in that they are human drugs and the methods used in, or the facilities or controls used for, their processing, packing or holding did not conform with CGMP regulation for drugs. The deviations documented during the inspection include the following:

- Failure to conduct repacking of penicillin and repacking of non-penicillin drugs in separate facilities;

- Failure to separate completely the air handling systems for the packing of penicillin products and non-penicillin beta-lactam drug products from non-penicillin drug products;

- Failure to provide assurance through drug testing that non-penicillin drug products had not been exposed to cross-contamination with penicillin; and,

- Failure to conduct stability studies or to have such studies conducted to justify the expiration dates that PharmPak, Inc. uses on solid oral dosage forms repacked into unit-for-use containers or to have data demonstrating the container/closure system used by PharmPak, Inc. is equal to or better than that used by the manufacturer, allowing use of the manufacturer's expiration date, or two years, whichever is shorter.

During the inspection of PharmPak, Inc. the firm did not have any stability data for solid oral dosage forms repacked in container and closure systems that are different from the original containers and closures to support the use of the manufacturers' expiration dates on the repackaged drug products. Moreover, the firm had not evaluated the original and repackaged container and closure systems for equivalency, in lieu of performing stability testing.

Local Repack Signs Consent Decree

On April 13, 2004, FDA announced the settlement of a court case against an Illinois firm involved in FDA's seizure of thousands of imported unapproved drugs, including those that were labeled in foreign languages and/or labeled as repacked.

The firm, Phil and Kathy's, Inc., a corporation doing business as Local Repack, Alliance Wholesale Distributor, and Local Pharmacy, signed on April 8, 2004, a Consent Decree in the U.S. District Court for the Northern District of Illinois agreeing to operate in full compliance with FDA's regulations. The signatories included Phillip R. Giannino, President, Phil and Kathy's, Inc. and Frank Weaver, the firm's head of repackaging operations.

FDA inspections in 2003 revealed that Phil and Kathy's, Inc. was importing and repacking drug products that were labeled in Spanish and Portuguese and not in accordance with FDA's approvals. In addition, the firm had repeatedly failed to comply with FDA's CGMP requirements, which serve to ensure that every marketed drug is safe, effective and properly manufactured.

Under the Consent Decree, Phil and Kathy's, Inc. is prohibited from manufacturing, labeling and distributing any article of drug until certain conditions are met, including that FDA has determined that the firm's repackaging operations comply with CGMP regulations. In addition, Phil and Kathy's, Inc. agreed not to repackage any foreign-labeled drugs or other drugs that are in any manner inconsistent with FDA's standards for approval. In case the firm purchases, distributes, or imports any such products, the Consent Decree gives the government additional authority to seek monetary damages.

The Consent Decree does not deal with the case involving Genendo Pharmaceutical, N.V., the importer of several drugs to Phil and Kathy's, Inc. which is still pending.

Illegal Importation of Prescription Drugs

FDA/CBP Import Blitz Exams Reveal Potentially Dangerous Illegally Imported Drug Shipments

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FDA and U.S. Customs and Border Protection (CBP) announced on January 27, 2004, that their second series of import blitz examinations found 1,728 unapproved drugs, including so-called "foreign versions" of FDA approved drugs, recalled drugs, drugs requiring special storage conditions, drugs requiring close physician monitoring and drugs containing addictive controlled substances.

These findings provide additional evidence of the serious risks posed by the illegal importation of prescription drugs. Unapproved drugs lack assurances of safety, effectiveness, quality and purity. Moreover, FDA cannot assure the safety and efficacy of a drug product the Agency has not reviewed and approved and when FDA has not

monitored the manufacturing and quality control processes of the facility in which the product was produced.

The blitz examinations were performed in November 2003 at the Buffalo, Dallas, Chicago, and Seattle mail facilities and the Memphis and Cincinnati courier hubs. FDA has been examining trends in the illegal importation of unsafe drugs since 2001, when it undertook a blitz examination at the Carson, California mail facility. In September 2003, FDA released the results of a similar study to the one contained in this announcement, and which had also been conducted in collaboration with CBP at the Miami, New York (JFK), San Francisco and Carson mail facilities in July and August, 2003. The most recent blitz marked the first time that imported drugs entering the U.S. through courier hubs were targeted in addition to those that pass through mail facilities.

Each of these studies has shown that the types of products that are imported into the U.S., as well as the countries from which they originate, vary depending upon the port and facility through which they enter. All of these studies have prompted the same safety concerns about the risks presented by imported drugs. Moreover, the information that FDA garnered will assist the Agency in doing a better job of quantifying the information obtained as a result of these studies, as well as the risks associated with imported drugs from foreign sources.

FDA and CBP inspectors examined a total of 1,982 parcels that appeared to contain drug products. The majority of the products found in the examined parcels were drugs. The parcels also contained other types of FDA-regulated products, such as dietary supplements and foods, as well as products not regulated by FDA, such as pens and notepads.

Parcels were examined irrespective of the country from which they were being exported. Canadian parcels appeared more frequently than parcels from any other country. Of the 1,006 parcels that entered through the mail facilities, FDA determined that approximately 80% of the parcels were exported from Canada, approximately 16% from Mexico, and the remaining 4% were exported from Japan, the Netherlands, and Taiwan.

The following are examples that are typical of the 1,728 unapproved drug products found during the blitzes and illustrate the potential risks they posed to their buyers:

Improperly Labeled Drugs: Many of the drugs did not bear adequate labeling or instructions for proper, safe use. For example, some products contained strictly foreign labeling, many contained dual labeling (in both English and a foreign language) and several contained no labeling whatsoever and were simply loose in plastic baggies or wrapped in tissue paper. Moreover, many of the imported drugs, including those from Canada, were shipped in containers which appeared to be intended for pharmacists without U.S. approved patient labels. This common problem is especially concerning in light of the special risks associated with many of the drugs noted below.

Controlled Substances: Ratio-Lenoltec with codeine, codeine, /*diazepam (Valium), lorazepam (Ativan), Tylenol 3 (containing codeine), and clonazepam are controlled substances that have abuse potential and can be dangerous when consumers take them inappropriately and without a physician's supervision.

Potentially Recalled Drugs: Serevent Diskus and Flovent Diskus medicines are used in the U.S. and Canada to treat asthma and chronic obstructive pulmonary disease. Flovent Diskus is approved in the U.S., but is not currently marketed in the U.S. The blitz results indicate that American consumers were sent these drugs from Canada. Shortly after the blitz operations, certain lots of the Canadian versions of these drugs were recalled in Canada. In the U.S., the import of these lots was the subject of an FDA consumer alert because of concerns that the product's delivery system might not function properly and might deliver too little of the drug - or none at all. Thus, at the time of importation, American consumers had no way of knowing if the Canadian products they were purchasing would subsequently be recalled. However, the FDA

approved product, sold in the U.S. through legitimate marketing channels, did not have the delivery system problem and was not subject to the recall.

So-Called "Foreign Versions" of FDA Approved Drugs: FDA approved versions of many of these products pose safety concerns that require use only under the close supervision of a health care professional. Variations from U.S. standards in potency and purity of unapproved versions may raise additional concerns regarding both safety and efficacy. Examples of these products include:

- **APO-Tamox** - an unapproved, foreign version of the anti-cancer drug tamoxifen;

- **APO-Warfarin** - an unapproved, foreign version of the blood thinner warfarin. The potency of warfarin may vary depending on how it is manufactured, and the drug must be carefully administered and monitored by a health professional in order to prevent serious bleeding problems;

- **APO-Carbamazapine** - an unapproved, foreign version of the anti-convulsant drug carbamazapine which requires initial screening and monthly monitoring of blood and platelet counts to ensure safe use;

- **APO-Allopurinol** - an unapproved, foreign version of a drug used in the management of certain types of cancer. Allopurinol, which requires periodic monitoring of kidney function during the first few months of treatment, can cause kidney failure with underlying renal disease;

- **Alti-Azathioprine** - an unapproved, foreign version of an immunosupressant drug. This drug can cause severe bone marrow depression and can be associated with an increased risk of infection and cancer development. FDA approved versions of this drug requires regularly scheduled monitoring of blood counts; and

- **Human Growth Hormone** - This is a widely used drug indicated for a number of conditions in both children and adults. It can have serious side effects (for example, it can unmask or worsen diabetes and cause an elevation of pressure in the brain) if used inappropriately or in excessive doses.

Drugs Requiring Risk Management and/or Restricted Distribution Programs: For example, Canadian-manufactured isotretinoin, a drug used to treat a severe form of acne, was shipped without any assurance that its use would be monitored by a physician. In the U.S., isotretinoin is subject to a stringent risk management plan, under which prescribers are required to screen, educate and monitor patients to avoid certain serious risks, such as birth defects that may occur following the use of the drug. U.S. prescribers are also expected to attest, prior to prescribing isotretinoin, that pregnancy testing has been done to confirm that the patient is not pregnant.

Drugs Requiring Initial Screening or Periodic Monitoring of Patients: Initial screening and periodic patient monitoring by a medical professional (for example,

monitoring liver function or blood parameters) are recommended in FDA's approved labeling for the following drugs which were found during the blitz operation:

- **Casodex** is used in the treatment of prostate cancer. A medical professional must rule out baseline liver disease prior to treatment initiation and should monitor liver function tests periodically during treatment;

- **Coumadin** and **Warfarin** are anticoagulants that require initial and periodic monitoring of blood parameters to avoid bleeding problems;

- **Clomid** is used in the treatment of ovulatory dysfunction. A medical professional must rule out liver, thyroid, and adrenal dysfunction before beginning treatment and should also perform monitoring during treatment to avoid ovarian hyperstimulation;

- **Metformin** is an oral hypoglycemic that requires regular monitoring of blood parameters and pre-treatment and ongoing assessments of kidney function to reduce the risk of development of lactic acidosis;

- **Tamoxifen** is a drug for which a medical professional must rule out uterine malignancy prior to, and regularly during treatment;

- **Amitriptyline** (Elavil) is an anti-depressant for which cardiovascular disorders must be ruled out prior to treatment;

- **Lithium Carbonate** is an anti-psychotic also used to treat manic depression. Individualized dosing and careful monitoring of serum levels is required for this drug to avoid life-threatening toxicity;

- **Drugs Requiring Careful Dosing:** For example, Synthroid (levothyroxine), Glucophage (metformin), Dilantin (phenytoin), digoxin, theophylline, Coumadin (warfarin) all require individualized titration of the dose prescribed and very careful dosing in order to avoid serious and potentially life-threatening side effects;

- **Drugs with Clinically Significant Drug-Drug Interactions:** Zocor (simvastatin), imipramine, Viagra (sildenafil citrate) and tramadol can be associated with clinically significant interactions with other drugs the buyer may be taking;

- **Biologic Drugs Which Should be Administered by a Healthcare Provider and are Not Licensed by FDA:** For example, Influenza Virus Vaccine approved in Canada but not licensed by FDA was encountered; and,

FDA Demonstrates Sale of Substandard Prescription Drugs from Bogus Canadian Website

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FDA Analysis of "Canadian Generics" Reveals the Drugs are Substandard and PotentiallyDangerous

FDA analysis of three commonly prescribed drugs marketed online as “Canadian Generics” demonstrated that the drugs were bogus, substandard, and potentially dangerous. One drug was a controlled substance. In light of these findings, FDA issued a press release that reiterated its strong concerns about purchasing prescription drugs online from unknown sources.

The products purchased were so-called generic versions of Viagra, Lipitor, and Ambien. None of the three products has a U.S.-approved generic version, and so all three drugs are unapproved for distribution in the U.S.

Ambien, a controlled substance (schedule IV), is approved for the short-term treatment of insomnia in the U.S. The product FDA obtained online was superpotent, including one tablet that contained nearly double the labeled amount of active ingredient. Taking

superpotent Ambien puts patients at risk for central nervous system depression, especially elderly or debilitated patients.

The so-called generic Lipitor that FDA purchased was subpotent, providing on average only 57 percent of the active ingredient claimed on the label. It also failed FDA's purity testing. Such subpotent products could present a long-term risk for the various complications of high cholesterol, such as heart disease. In addition, the so-called generic Lipitor product was sold to FDA's online purchaser, although the purchaser said that he was taking the antibiotic Erythromycin. Lipitor's label warns against taking Lipitor and Erythromycin at the same time.

Viagra is sold in the U.S. to treat impotence. The so-called generic version of this product contained too little of the active ingredient, failed the dissolution test, and had an unacceptable level of impurities.

The purchase and analysis of these drugs demonstrates that buying prescription drugs online from unknown foreign sources can be a risky business. Even when a website looks legitimate, it may dispense unapproved and misbranded drugs that are not the same quality as FDA-approved products sold in the United States. Consumers who believe that they are getting equivalent products from reputable sources may be misled, putting their health at risk.

Warning Letter Issued to Expedite-Rx

Warning Letter Issued to Individuals Who Assisted U.S. Consumers in Obtaining Rx Drugs From Canada

On January 22, 2004, FDA's CDER issued a Warning Letter to Mr. Noel Thomas, Curb, R.Ph., Expedite-Rx, SPC Global Technologies, Ltd., Temple, Texas; Mr. Tom Lanham, Expedite-Rx, Employer Health Options, Inc.; and Mr. Mike Strickland, President, Employer Health Options, Inc., Scottsboro, Alabama.

The Warning Letter noted that FDA had learned that the above-named individuals had been assisting U.S. consumers in obtaining prescription drugs from Canada through Expedite-Rx, SPC Global Technologies, Ltd., and Employer Health Options, Inc. Specifically, these firms were running a program that facilitated the importation of prescription drugs from Canada for U.S. consumers. The Warning Letter further advised that these, "… actions violate the Act, 21 U.S.C. 301 et seq." Furthermore, these actions also present a significant risk to public health, and mislead the public about the safety of the drugs that are obtained through this program.

Virtually every shipment of prescription drugs from Canadian pharmacies to consumers in the U.S. violates the Act. Even if a prescription drug is approved in the U.S., if the drug is also originally manufactured in the U.S., it is a violation of the Act for anyone other than the U.S. manufacturer to import the drug into the U.S. Moreover, drugs shipped into the U.S. from Canadian pharmacies are generally unapproved, labeled incorrectly, and/or dispensed without a valid prescription. Thus, their shipment into the U.S. from Canada violates the Act.

The Expedite-Rx Internet website http://www.expedite-rx.com, misleadingly states, "In a published statement an FDA spokesman said that the federal government has not enforced any existing laws affecting such importation in years, and that it has instead taken a compassionate approach (to enforcement) (that is) intended to help people with serious health problems." FDA advised in the Warning Letter that the above statement is misleading. Under FDA's Personal Importation Policy, as a matter of enforcement discretion in certain defined circumstances, FDA allows consumers to import otherwise illegal drugs. However, this policy is not intended to allow importation of foreign versions of drugs for which there is an FDA approved version.

FDA is very concerned about the importation of prescription drugs from Canada and other foreign countries because, in the Agency's experience, many drugs obtained from foreign sources that purport or appear to be the same as U.S.-approved prescription drugs are, in fact, of unknown quality. Recent examples of counterfeit products entering the U.S. marketplace also raise substantial safety questions about drugs from foreign countries.

Moreover, there is a possibility that drugs, which come to U.S. consumers through Canada or purport to be from Canada, may not actually be Canadian drugs. In short, drugs delivered to the American public from foreign countries may be very different from products approved by FDA and may not be safe and effective. For all of these reasons, FDA believes that operations such as Expedite-Rx expose the public to significant potential health risks.

FDA Takes Action Against Foreign Websites
Selling Counterfeit Contraceptive Patches

FDA announced on February 12, 2004, that the Agency had taken action against three foreign Internet websites associated with a site previously found to be selling counterfeit contraceptive patches that contain no active ingredients. These counterfeit patches provide no protection against pregnancy.

The three newly discovered Internet websites involved were www.usarxstore.com, www.europeanrxpharmacy.com, and www.generic.com. These websites also sold other drugs that purported to be the same as FDA approved drugs, but were in fact from unknown sources and of unknown safety and efficacy. To protect the public health FDA obtained the cooperation of the U.S.-based Internet service provider in shutting down service to these websites.

This action follows similar action FDA took against www.rxpharmacy.com, which sold counterfeit contraceptive patches as well as other products that purport to be versions of FDA approved drugs.

FDA urged consumers to treat any drugs purchased from these websites as suspect, and not to be considered safe or effective. Consumers who have products purchased from any of these websites should not use them, but instead contact their healthcare providers immediately.

The counterfeit contraceptive patches were promoted as Ortho Evra transdermal patches, which are FDA approved, and made by Ortho-McNeil Pharmaceutical, Inc. Instead customers received packages of patches without the active ingredient necessary to make the patches effective. Moreover, the counterfeits were sent in simple plastic zip-lock bags without identifying materials, lot numbers, expiration dates or any other labeling information needed to safely and effectively use this prescription product.

Details of the differences between the counterfeit contraceptive patch and the authentic Ortho Evra contraceptive patch were described in another news release, which can be viewed at: http://www.fda.gov/bbs/topics/NEWS/2004/NEW01017.html. Photos contrasting the legitimate contraceptive patch with the counterfeit are on display at FDA's website:
http://www.fda.gov/bbs/topics/news/photos/contraceptive/counterfeit.html.

FDA Issues Warning Letter to West Virginia Business Offering Illegal Foreign Drugs

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On February 20, 2004, FDA announced that the Agency had issued a Warning Letter to Discount Prescriptions from Canada, Inc., a Fairview, West Virginia business operation that helped its customers import illegal prescription drugs from a Canadian pharmacy. The letter informed the company that the Agency had determined that their operation is in violation of the Act.

The Warning Letter noted that statements on the firm's website, through which the drugs were being sold, were misleading because they led U.S. consumers to believe that drugs imported from Canada are as safe as domestically dispensed prescription drugs. In fact, prescription drugs purchased from foreign countries generally are not FDA approved, do not meet FDA standards, and do not have the same assurance of safety as drugs regulated by FDA.

The letter also noted that unapproved drugs coming into the U.S. through Canada, or purportedly from Canada, may not actually be Canadian drugs. Recent examples of counterfeit products entering the U.S. marketplace also raise substantial safety questions about drugs from foreign countries. Drugs delivered to the American public from foreign countries may be very different from products approved by FDA and may not be safe and effective. FDA believes that operations such as Discount Prescriptions from Canada, Inc., therefore expose the public to significant potential health risks.

FDA continues to find numerous safety problems relating to prescription drugs being mailed into the U.S. from Canada without effective regulatory oversight. For example, recently officials from the state of Minnesota evaluated eight Canadian pharmacies that send drugs to the U.S. They found 32 distinct violations of safe pharmacy practice, including the following:

- One pharmacy had no policy in place for drug recalls. Representatives allegedly said that patients could contact the pharmacy about a recall "if they wished;"

- Some pharmacies did not check patient profiles for allergies; and,

- A number of pharmacies dispensed grossly improper amounts of medications.

At least one pharmacy provided drugs that apparently were not of Canadian origin.

In contrast to its role in assuring the safety of prescription drugs distributed in the U.S., FDA has no way to assure the safety of drugs supplied by these Canadian pharmacies.

FDA's Warning Letter also refuted misleading claims by the company that such unapproved foreign drugs can be legally imported into the country. The letter made it clear that drugs lacking the safeguards provided by the Act cannot be substituted for approved drugs of known safety and efficacy. In response to the Agency's Warning Letter, the firm ceased operations.

Rx Depot Agrees to Consent Decree of Permanent Injunction

Defendants Admit Liability for Causing the Illegal Importation of Unapproved New Drugs and U.S. Manufactured Drugs

On August 20, 2004, FDA announced the filing of a Consent Decree of Permanent Injunction against Rx Depot, Inc., Rx of Canada, LLC, and individual officers based on violations of the Act. In the Consent Decree, the firms and corporate officers Carl Moore and David Peoples admitted liability for causing the importation of unapproved new drugs and U.S.-manufactured drugs in violation of the Act and agreed to permanently cease such activities.

The defendants caused the illegal importation of prescription drugs from Canada. The defendants accepted prescriptions from U.S. customers, sent these to a Canadian pharmacy partner, and received a commission from the Canadian pharmacy when the pharmacy sent prescription drugs directly to the U.S. customers.

The Department of Justice's Office of Consumer Litigation, and the U.S. Attorney's Office for the Northern District of Oklahoma filed the Consent Decree in the U.S. District Court for the Northern District of Oklahoma. The defendants agreed to this Consent Decree following an evidentiary hearing and a November 6, 2003 Preliminary Injunction Order that preliminarily prevented them from causing the importation of or profiting from the sale of any unapproved new drugs, misbranded drugs, or U.S.-manufactured drugs.

In the Consent Decree, the defendants represent that Rx Depot, Inc. and Rx of Canada, LLC, have permanently ceased operations and that all defendants, including Moore and Peoples, have ceased causing the importation of unapproved new drugs, misbranded drugs, and U.S.-manufactured drugs or receiving a commission from these activities. The Consent Decree also permanently restrains all defendants from any illegal importation of prescription drugs. Finally, the Consent Decree provides FDA with inspection authority to ensure compliance and penalizes the defendants $4,000 per day for any violation of the Consent Decree.

The defendants' businesses posed a significant public health threat because unapproved drugs that are imported from foreign countries and U.S.-manufactured drugs that are imported back into the U.S. by parties other than the U.S. manufacturer do not have the same assurance of safety and efficacy as drugs that are regulated by FDA.

Because these drugs are not subject to FDA oversight and are not continuously under the custody of a U.S. manufacturer or authorized distributor, their quality is unpredictable.

They could be outdated, contaminated, counterfeit, or contain erratic amounts of the active ingredient or different excipients. Also, the drugs may have been held under uncertain storage conditions that may have had a deleterious effect on their therapeutic use.

Internet Enforcement Activities

Human Growth Hormone Promoted on the Internet

> Title 21 U.S.C. 333(e)(1) states that, " . . .whoever knowingly distributes, or possesses with intent to distribute, human growth hormone for any use in humans other than the treatment of a disease or other recognized medical condition, where such use has been authorized by the Secretary of Health and Human Services under 21 U.S.C. 355 and pursuant to the order of a physician, is guilty of an offense punishable by not more than 5 years in prison, such fines as are authorized by Title 18 U.S.C. or both."

On February 18, 2004, FDA's Dallas District Office issued a Warning Letter to Tony Stires, Global Internet Alliance, Corpus Christi, Texas. The Warning Letter concerned T-10 HGH, Human Growth Hormone, marketed by Global Internet Alliance as shown on the Internet website www.ezsuoer.com. According to information on this site, T-10 HGH was being sold as an anti-aging treatment regimen. Ordering instructions for the drug were provided on the website.

The T-10 HGH formula was described on the firm's Internet website as "Sublingual T-10 HGH is sprayed directly into the mouth three times a day and is absorbed directly into the mucus membrane," and "T-10 HGH - Real Recombinant Growth Hormone - 30 ml (1 fl. oz) - one month supply per bottle 600 nanograms per milliliter!"

The intended anti-aging treatment and disease treatment claims for T-10 HGH were conveyed on Global Internet Alliance's Internet website. These included statements such as:

- HGH restores muscle mass;
- HGH decreases body fat;
- HGH increases sexual function;
- HGH thickens the skin, reducing wrinkles;
- HGH restores lost hair;

- HGH improves cholesterol profile;
- HGH improves vision;
- HGH improves memory; and,
- HGH elevates mood and improves sleep.

FDA approved growth hormone as a new drug in 1940. Growth hormone was not marketed as a dietary supplement, nor as a food, before being approved as a drug. Therefore, growth hormone is excluded from the definition of a dietary supplement under 21 U.S.C. 321(ff)(3)(6) of the Act because growth hormone is an article approved as a new drug under 21 U.S.C. 355.

The Warning Letter advised Mr. Stires that:

> "Based on the claims cited above, T-10 HGH is a 'drug' as defined by 21 U.S.C. 321(g). Moreover, T-10 HGH is a 'new drug' as defined by 21 U.S.C. 321(p) because there is no evidence that it is generally recognized as safe and effective for these intended uses. Under 21 U.S.C. 355(a), a 'new drug' may not be introduced or delivered for introduction into interstate commerce unless an FDA approved new drug application (NDA) is in effect for such drug. The continued distribution of this product without an approved NDA violates 21 U.S.C. 355."

The Warning Letter also noted that T-10 HGH is misbranded because its labeling fails to bear adequate directions for the uses for which it is being offered and it is not exempt from this requirement since it is an unapproved new drug.

In addition, the letter stated that distribution of T-10 HGH violates 21 U.S.C. 333(e)(1) because this growth hormone is being promoted and distributed on Global Internet Alliance's Internet website for an unapproved use. There are no recombinant human growth hormone (somatotropin) products that are approved by FDA for anti-aging treatment.

Internet Firm Promoting "Antivirals"

Firm Warned for Marketing Unapproved New Drugs on Internet Website

On June 21, 2004, FDA's Seattle District Office issued a Warning Letter to Richard Hicks, Freedomantiviral, Kirkland, Washington. The Warning Letter concerned the firm's marketing of the products, Fix-It Antiviral, Fix-it Oral Antiviral, Pre-Fix Invisible Condom, and Acyclovir.

A review by FDA of the firm's Internet website www.freedomantiviral.com disclosed that Fix-It Antiviral was being sold as a topical antiviral drug product for the treatment of herpes; Fix-it Oral Antiviral was marketed as an oral antiviral drug product for the

treatment of herpes, flu, cold, and other viral infections; and Pre-Fix Invisible Condom was being sold as a topical antiviral for the prevention of sexually transmitted diseases such as human immunodeficiency virus (HIV), herpes, human papilloma virus (HPV), gonorrhea, chlamydia, genital warts, and other sexually transmitted diseases.

The firm was also offering the product Acyclovir, an approved antiviral prescription drug for the treatment of herpes, chickenpox, shingles, and other conditions, without a prescription.

Freedomantiviral stated on its Internet website that Fix-It Antiviral Cream "Heals and prevents herpes outbreaks," and that "Fix-It Antiviral Heroes Treatment is a topical antiviral cream that penetrates deep into the dermis and inactivates the herpes virus within human cells."

Regarding Pre-Fix Invisible Condom, Freedomantiviral's Internet website stated, "Pre-Fix is a high quality anti-viral sexual lubricant gel that helps to prevent the transmission of all sexually transmitted diseases, including HIV and herpes. Pre-Fix also acts as a spermicide."

In addition, Freedomantiviral's Internet website stated that "Acyclovir is an antiviral used to treat shingles, chickenpox, or genital herpes. It may also be used to treat other conditions."

The Warning Letter advised the firm that Fix-It Antiviral, Fix-it Oral Antiviral, and Pre-Fix Invisible Condom are "drugs" because they are promoted to cure, mitigate, treat, or prevent disease. Moreover, these products are "new drugs" because there is no evidence that they are generally recognized as safe and effective for their intended uses.

The distribution of Fix-It Antiviral, Fix-it Oral Antiviral, and Pre-Fix Invisible Condom for these intended uses without an approved NDA violates the Act. Furthermore, the conditions for which these products are offered were not amenable to self-diagnosis and treatment by individuals who are not medical practitioners; therefore, adequate directions for use could not be written so that a layman could use these drugs safely for their intended purposes. Thus, all three products' labeling failed to bear adequate directions for their intended uses, causing them to be misbranded.

Warning Letter Issued for Website Promoting Unapproved "Drugs"

On September 23, 2004, FDA's Denver District Office issued a Warning Letter to Thomas J. Clark, CEO, Evercrete International, d/b/a T.J. Clark & Company, Inc., Saint George, Utah. The Warning Letter advised the

firm that FDA had reviewed the firm's Internet websites http://www.tjclarkminerals.com, http://www.tjclarkinc.com, http://www.tjclarkco.com, http://www.tjclark.com, http://www.tjclarkdirect.com, and http://www.t-j-clark.com. The Warning Letter advised Mr. Clark that this review showed serious violations of the Act in the labeling of nineteen of the firm's products. The Warning Letter noted that, under the Act, articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man are drugs. FDA advised Mr. Clark that an FDA review of the firm's Internet website disclosed that the website makes claims that their products are useful in the prevention, treatment, and mitigation of diseases.

The Warning Letter added that, "These claims cause your products to be drugs, as defined in Section 201(g)(1)(B) of the Act. Because these products are not generally recognized as safe and effective when used as labeled, they are also new drugs. Under Section 505 of the Act, a new drug may not be legally marketed in the U.S. without an approved NDA."

Some of the products and objectionable claims include the following:

- *T.J. Clark's Catalyzed Melatonin*:

  "Melatonin...appears to be the body's natural defense against breast cancer." "[M]elatonin can be beneficial in treating children who have sleep disorders associated with autism, epilepsy, Down's syndrome and cerebral palsy." "Another important ingredient of our melatonin is L-Glutamine. L-Glutamine supplements can be helpful in the treatment of arthritis, autoimmune diseases, fibrosis, intestinal disorders, peptic ulcers, connective tissue diseases, and tissue damage due to radiation treatment for cancer… It has been used to treat problems such as epilepsy…impotence, schizophrenia…"

- *T.J. Clark Liquid Co-Q10 Advanced Formula*:

  "[A] very beneficial supplement for individuals who suffer from disorders of the cardiovascular system..."

  "Revive failing hearts... Lower blood pressure"

- *T.J. Clark's Catalyzed Vitamin E*:

  "[F]ights cancer and cardiovascular disease"
  "[R]educes DNA damage in cells that can lead to mutations and cancer"
  "[C]an improve chronic fatigue syndrome"
  "[M]ay ease angina and arthritis pain"
  "[B]oosts HDL levels (the lipoprotein that carries cholesterol away from the cell)"

Over-the-Counter Products

Firm Warned that Antimicrobial Lotion is a New Drug

On June 23, 2004, FDA's Cincinnati District Office sent a Warning Letter to C & K Manufacturing & Sales Co., LLC (C & K), Westlake, Ohio, citing unapproved new drug violations related to their antimicrobial lotion, Derm-Care AL.

The letter advises the firm that the product is not deferred to FDA's OTC Drug Review. The labeling for Derm-Care AL includes such claims as: "long-lasting, broad spectrum antimicrobial lotion," and ". . . keeps on killing [pathogens] for up to 4 hours." The labeling also represents this product as effective against "Norovirus," "Hepatitis A . . . B . . . [and] C," "Methicillin-resistant Staph aureus," among other pathogens, and states that the product's antimicrobial effectiveness is not diminished by contact with water or by handwashing ("does not lose effect, even if hands become wet," "remains after handwashing"). These claims have never been evaluated in the development of any OTC drug monograph. Therefore, the safety and efficacy of this product for these indications has not been established.

Other manufacturers of OTC skin protectants comply with the final monograph for those products (68 FR 33362, 6/4/03) and FDA's policy allows continued marketing of OTC drugs legitimately deferred to ongoing rulemakings. The marketing of this product therefore threatened the OTC Drug Review and the new drug approval processes. C & K promoted Derm-Care AL for its purported long-lasting antimicrobial efficacy that is unaffected by hand washing or contact with water. Such claims may lead to a false sense of security resulting in infrequent hand washing, which is the principal method for protecting against pathogens and cross-contamination in high soil and high bio-burden environments.

Firm Warned that its OTC Drugs are New Drugs and Misbranded

On April 29, 2004, FDA's Kansas City District Office sent a Warning Letter, to Vita-Erb Ltd., Springfield, Missouri, citing unapproved new drug, Section 505, and misbranded drug violations, Section 502, for various OTC oral and topically applied drug products.

The Warning Letter advised that certain orally administered and topically applied OTC drug products were being marketed in violation of the new drug provisions of the Act. The orally administered drugs are offered for serious disease conditions, namely cancer prevention. Except for one of the topicals, the products were also misbranded under one or more provisions of Section 502.

Two of the topicals violated the final OTC drug monograph covering antidandruff preparations and fail to bear adequate directions for use and warnings required by that monograph. One of the topicals contains hydrocortisone, but failed to satisfy FDA's enforcement policy for marketing products with this active ingredient. The remaining topicals could not be deferred to FDA's OTC Drug Review because they did not have the marketing history in the United States required for inclusion in the OTC Drug Review.

FDA Announces Recall of "DU" Brand
Nasal Decongestant Due To Possible Health Risk

Nasal Spray Found Contaminated with *Burkholderia cepacia*

On May 14, 2004, FDA alerted consumers not to purchase or use a recalled lot of DU brand nasal decongestant spray (distributed by Drugs Unlimited, Puerto Rico) because it may be contaminated with **Burkholderia cepacia** - a bacterium that could cause serious, potentially life-threatening infections in some patients. Individuals with compromised immune systems, especially those with cystic fibrosis, could be at risk.

The recalled product was being sold OTC in 15 milliliter (or "1/2 ounce") and 30 milliliter bottles labeled "DU 12-Hour Nasal Spray" with the lot number J4492 imprinted at the bottom of the carton and the back of the bottle label. The recalled product also bore an expiration date of September 2006.

The product appeared to have been distributed throughout Puerto Rico and it is likely linked to an earlier recall of other contaminated product lots that were sold to other distributors.

FDA advised consumers who may have used the recalled product to consult their physicians. Consumers who may still have had the recalled product were advised not ti use it, but **instead** to return it immediately to the store where it was purchased.

Propharma, Inc. Recalls "Twice-A-Day 12 Hour Nasal Spray"

On March 18, 2004, Propharma, Inc., Miami, Florida announced that the firm was recalling "Major Twice-A-Day 12 Hour Nasal Spray - Nasal Decongestant, 1/2 oz. bottle, Lot #K4496, Exp 10/06 because the lot was contaminated with a type of bacteria called ***Burkholderia cepacia.*** Use of this contaminated product could cause serious or potentially life-threatening infections in patients with compromised immune systems, particularly individuals with cystic fibrosis.

This product is a nasal decongestant containing the active ingredient oxymetazoline hydrochloride 0.05%, the lot number and expiration date are found on the bottom of the carton and the back of the bottle label.

The entire lot had been distributed nationwide to wholesalers, pharmacies, hospitals and retailers by Major Pharmaceuticals, Livonia, Michigan. Major Pharmaceuticals initiated a recall to the consumer level.

Propharma was alerted to this problem following reports of infections and findings of Burkholderia cepacia in the nasal spray by a hospital in Colorado. FDA sample analysis confirmed the presence of the bacteria in unopened bottles from the affected lot.

Firm Warned that OTC Drugs are New Drugs

Warning Letter Advises Firm that "Old Hickory Athlete's Foot & Ringworm Remedy" and Other OTC Products are "Unapproved New Drugs

On April 21, 2004, FDA's New Orleans District Office issued a Warning Letter to Kenneth H. Grissett, President, Old Hickory Medicine Company, Inc. (Old Hickory), Andalusia, Alabama. An FDA investigator conducted an inspection of the firm on November 18 - 20, 2003.

The FDA investigator documented deviations from the regulations that cause the firm's finished drugs to be adulterated and misbranded under the Act.

In addition, the firm was distributing unapproved new drugs in violation of Section 505(a) of the Act. The investigator found that Old Hickory was manufacturing labels, and distributing human drug products, including "Old Hickory Ear Drops," "Old Hickory Foot-O-Latum," "Old Hickory Athlete's Foot & Ringworm Remedy," and "Old Hickory Athlete's Foot & Ringworm Liquid."

The Warning Letter advised the firm that because of the firm's deviations from applicable regulations "Old Hickory Ear Drops," "Old Hickory Foot-O-Latum," "Old Hickory Athlete's Foot & Ringworm Remedy," and "Old Hickory Athlete's Foot & Ringworm Liquid" are considered new drugs. Therefore, they may not be introduced or delivered into interstate commerce without approved NDAs. These products also are misbranded in that their directions for use deviate from the language of the applicable monographs. Likewise, the products are misbranded for failure to bear required warnings.

In addition, each label for the above-mentioned products failed to comply with the regulations covering the format and content of OTC drug labeling. These regulations establish the criteria for ensuring that OTC drug labeling information is conspicuous at the time of purchase and use. The failure to comply with these regulations caused these OTC drug products to be misbranded.

In addition to deviations from the requirements of the Act discussed above, the FDA investigator documented deviations from the CGMP regulations. The CGMP deviations documented during the inspection included, but were not limited to, the following:

- Failure to perform finished product testing prior to release of drug products for distribution to determine satisfactory conformance to the final specifications, identity, and strength of each active ingredient;

- Failure to established written procedures to prevent objectionable microorganisms in finished drug products and failure to perform microbial testing on each batch of finished drug product;

- Failure to conduct assays or identify mixing times nor heating temperatures used to manufacture drug products to assure uniformity and homogeneity; and,

- Failure to keep records documenting the maintenance and cleaning of equipment.

Pharmacy Compounding

Section 127 of the FDA Modernization Act of 1997 amended the Act by adding section 503A, which specified certain conditions under which compounded human drugs could be exempt from particular requirements of the Act. In April 2002, however, the U.S. Supreme Court struck down the commercial speech restrictions in Section 503A of the Act as unconstitutional. Accordingly, all of Section 503A is now invalid.

As a result, FDA now utilizes its longstanding policy of exercising its enforcement discretion regarding certain types of pharmacy compounding. This policy is articulated in Compliance Policy Guide (CPG) Section 460.200, issued on June 7, 2002. The CPG contains factors that the Agency considers in deciding whether to exercise its enforcement discretion.

One factor is whether a firm is compounding finished drugs from bulk active ingredients that are not components of FDA approved drugs without an FDA sanctioned IND application, as required by 21 U.S.C. 355(i) and 21 CFR Part 312. Another factor is whether a firm is compounding drugs that are "versions" of drugs that were withdrawn or removed from the market for safety reasons. The factors listed in the CPG are not intended to be exhaustive, and other factors may also be appropriate for consideration, including factors that indicate that a compounded product may have a potential adverse effect on the public health.

Domperidone

In June 2004, in response to reports that women may be using an unapproved drug, domperidone to increase lactation, the agency issued a talk paper warning breastfeeding women not to use this product because of safety concerns. FDA also issued four Warning Letters and two untitled letters to pharmacies that compound products containing domperidone and firms that supply domperidone for use in compounding. FDA also issued an import alert to FDA field personnel regarding detention and refusal of domperidone offered for import.

FDA took these actions because of its safety concerns about domperidone from compounding pharmacies and sources in foreign countries. Although domperidone is approved in several countries outside the U.S. to treat certain gastric disorders, it is not approved in any country for enhancing breast milk production in lactating women and it is not approved in the U.S. for any indication.

The agency is concerned with the potential public health risks associated with domperidone. There have been several published reports and case studies of cardiac arrhythmias, cardiac arrest, and sudden death in patients receiving an intravenous form of domperidone that has been withdrawn from the market in a number of countries. In several countries where an oral form of domperidone continues to be marketed, labels for the product contain specific warnings against use of domperidone by breastfeeding women and note that the drug is excreted in breast milk and could expose a breastfeeding infant to unknown risks. Because of the possibility of serious adverse effects, FDA recommends that breastfeeding women not use domperidone to increase milk production.

The letters issued by FDA state that all drug products containing domperidone (whether compounded or not) violate the Act because they are unapproved new drugs and misbranded. In addition, distribution within the U.S., or importation of domperidone-containing products, violates the law. The four Warning Letters are discussed in detail below.

Domperidone Warning Letters

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Hopewell Pharmacy

On June 7, 2004, FDA's New Jersey District Office issued a Warning Letter to Gene Ragazzo, R.Ph., and James Palmieri, R.Ph., Co-Owners of Drugs Are Us, Inc., d/b/a/ Hopewell Pharmacy, located in Hopewell, New Jersey. On October 8 - 24, 2003, investigators from FDA and the New Jersey Board of Pharmacy inspected Drugs Are Us, Inc. The inspection revealed that Drugs Are Us, Inc. was preparing and distributing domperidone 5mg, 10mg, 20mg, 30mg, 40mg capsules and 1 mg/ml and 10mg/ml liquid suspension for human use.

In the Warning Letter FDA advised Drugs Are Us, Inc., that the Agency is concerned with the public health risks associated with the compounding of domperidone. FDA warned the firm regarding the use of domperidone in compounding. FDA also noted that the firm was compounding drug products containing polidocanol, which is also not an active ingredient contained in any FDA approved drug product.

FDA advised that all products compounded by Drugs Are Us, Inc. containing domperidone and polidocanol are drugs under Section 201(g) of the Act and because they are not generally recognized by qualified experts as safe and effective for their labeled uses, the products are new drugs. No approved application is in effect for these products. Accordingly, their introduction or delivery for introduction into interstate commerce violated the Act. These products are also misbranded, because they do not bear adequate directions for use and they are not exempt from this requirement.

Drugs Are Us, Inc.'s Internet website also identified adenosine monophosphate as a product that the firm offers to compound. The Warning Letter advised the firm that drugs containing adenosine monophosphate were removed from the market in 1973, because they were determined to be neither safe nor effective. The firm violates the Act if it compounds such products.

In addition, Drugs Are Us, Inc.'s Internet website also contains a list of injectable products that the firm offers to compound, including human growth hormone. Title 21 U.S.C. 333(e) states that, "whoever knowingly distributes, or possesses with the intent

to distribute, human growth hormone for any use in humans other than the treatment of a disease or other recognized medical condition, where such use has been authorized by the Secretary of Health and Human Services under 21 U.S.C. 355 and pursuant to the order of a physician, is guilty by not more than 5 years in prison, such fines are authorized by Title 18 U.S.C. or both." FDA advised that compounding human growth hormone for anti-aging treatment or any other unapproved use violates 21 U.S.C. 333(e).

Axium Pharmacy

On June 7, 2004, the Florida District issued a Warning Letter to James Summerville, President of Axium Healthcare Pharmacy, located in Altamonte Springs, FL. On February 10-12, 2004, investigators from FDA, the Florida State Bureau of Pharmacy Services, and the Florida State Investigative Services inspected the firm. This inspection revealed that the firm compounded human prescription drugs in various strengths, including domperidone and ribavirin capsules.

FDA issued a Warning Letter similar to the Drugs Are Us, Inc. letter, advising the firm that the Agency is concerned with the public health risks associated with domperidone and warning the firm that it is illegally introducing unapproved and misbranded drugs into interstate commerce.

FDA also advised Axium Pharmacy that it does not condone the firm's compounding of ribavirin 400 mg and 600 mg capsules. Ribavirin is commercially available as FDA-approved 200 mg tablets and capsules. A 400 mg or 600 mg compounded capsule is essentially a copy of a commercially available product because the patient could simply take two or three commercially available 200 mg tablets or capsules instead of the compounded product.

Peoples Pharmacy

On June 7, 2004, FDA's Dallas District Office issued a Warning Letter to Bill Swail, President of Peoples Pharmacy, located in Austin, Texas. On April 14-17, 2003, investigators from the FDA and the Texas State Board of Pharmacy inspected the firm. This inspection revealed that the firm compounds and distributes 5mg, 10mg, 20mg, 30mg, and 40 mg domperidone capsules for human use.

FDA issued a Warning Letter similar to the Drugs Are Us, Inc. and Axium Pharmacy letters, advising the firm that the Agency is concerned with the public health risks associated with domperidone and warning the firm that it is illegally introducing unapproved and misbranded drugs into interstate commerce.

FDA also advised Peoples Pharmacy that it was very concerned about the injectable drug product betamethasone acetate/betamethasone phosphate, compounded and distributed by the firm without the necessary controls to ensure drug product sterility and potency. The Warning Letter acknowledged that the firm, at the conclusion of the inspection, had agreed to correct these deficiencies.

FDA noted in the Warning Letter that the firm's "Formula File" contained formulas for cisapride capsules and cisapride suspension. Cisapride was removed from the market for safety reasons and as such, FDA will not exercise its enforcement discretion to permit compounding of cisapride products for human use.

Spectrum Chemicals

On June 7, 2004, FDA's New Jersey District Office issued a Warning Letter to Paul Berg, President of Spectrum Chemicals and Laboratory Products, located in Gardena California. On January 29–February 5, 2004, FDA investigators inspected the firm, located at 755 Jersey Avenue, New Brunswick, New Jersey. The firm receives active pharmaceutical ingredients (APIs) from manufacturers and distributors. These APIs are subsequently repackaged and relabeled for further distribution to pharmacies for compounding.

The inspection revealed that the firm was repacking and distributing the bulk API domperidone for use in pharmacy compounding.

The Warning Letter advised that the Agency is concerned with the public health risks associated with the compounding of domperidone and warned the firm regarding the use of domperidone in compounding. FDA advised the firm that the domperidone that it repacks and distributes to pharmacies for compounding violates section 502(f)(1) of the Act.

Warning Letter Issued for Compounding Fentanyl Lollipops

Plum Creek Pharmacy

Labeling Fails to Disclose Risk of Fentanyl "Lollipops"

On October 7, 2003, FDA's Dallas District Office issued a Warning Letter to John Rains, R. Ph., CEO, of Plum Creek Pharmaceuticals, Inc., located in Amarillo, Texas. On February 24-28, 2003, investigators from FDA and the Texas State Board of Pharmacy conducted an inspection of the firm. This inspection disclosed that the firm compounds various veterinary and human prescription drugs, including Fentanyl with Naloxone "lollipops," and Fentanyl with Naloxone and

Midazolam “lollipops” in various strengths. These “lollipops” are used for pain management, often for end-stage cancer patients.

The Warning Letter advised the firm that the Agency is seriously concerned about the public health risks associated with the compounding of "lollipops" that contain Fentanyl and Naloxone and Fentanyl, Naloxone, and Midazolam, especially when such products are prepared for dispensing to patients without labeling and other packaging and safety features required by FDA for the approved Fentanyl “lollipops”.

The letter advises the firm that its compounded Fentanyl with Naloxone, and Fentanyl with Naloxone and Midazolam “lollipops,” are misbranded within the meaning of section 502(a) of the Act because the products’ labeling is false and misleading. The labeling fails to reveal consequences that may result from the use of the article under conditions of use prescribed in the labeling or under such conditions of use as are customary or usual. The lollipops are also misbranded within the meaning of section 502(f)(2) because their labeling does not provide adequate warnings against use by children, where its use may be dangerous to health. These products are further misbranded within the meaning of section 502(j) in that they are dangerous to health when used in the manner prescribed in their labeling.

The Warning Letter also addressed Plum Creek’s compounding of veterinary prescription drug products from bulk active pharmaceutical ingredients. The firm was advised that the veterinary drugs compounded and distributed were new animal drugs within the meaning of Section 201(v) of the Act. These drugs were adulterated under Section 501 (a)(5) of the Act because they are unsafe within the meaning of Section 512 of the Act. Under Section 512, a new animal drug is deemed to be unsafe unless an approved New Animal Drug Application (NADA) is in effect for the specific product in question. None of the animal drugs compounded and distributed by Plum Creek are the subject of an approved NADA.

Contaminated/Subpotent Compounded Drugs

Warning Letter Issued to Lee Pharmacy

FDA Inspection Finds Mold on Open Vials of Methyprednisolone Acetate Injection

On October 7, 2003, FDA’s Dallas District Office issued a Warning Letter to Warren B. Lee, President of Lee Pharmacy, located in Fort Smith, Arkansas. On December 11-13, 2002, investigators from the FDA inspected Lee Pharmacy as authorized by an Inspection Warrant filed in the United States District Court for the Western District of Arkansas.

The Warning Letter included new animal drug/adulteration charges and an informational section advising the firm about the analyses of samples of the compounded human drugs Methyprednisolone Acetate Injection and Triamcinolone Acetonide Injection, collected during the December 2002 inspection.

FDA analysis of the firm's Methylprednisolone Acetate Injection confirmed the presence of Penicillium rugulosum. Consistent with this analysis, FDA observed mold on open vials of the same lot collected from the clinic of the consumer who complained to FDA. FDA acknowledged that Lee Pharmacy recalled all preservative free injectables compounded in year 2002, which included this lot. FDA advised the firm that the lot of Methylprednisolone Acetate injection violated Section 501(a)(1) of the Act, in that it consisted in whole or in part of a filthy, putrid, or decomposed substance. FDA also collected a sample of the firm's Triamcinolone Acetonide for Injection. The sample was tested for potency and was found to be sub-potent. FDA advised the firm that the lot of Triamcinolone Acetonide Injection, which had expired, violated Section 501(c) as labeled, or 501(b) if it is a suspension product (as the label and formulation imply), in that the strength differs from that which it purports or is represented to possess.

Warning Letter Issued for Inhalation Compounding

Monsserrat Pharmaceuticals

On January 20, 2004, FDA's San Juan District Office issued a Warning Letter to Ambrosio Malave, President of Monserrat Pharmaceuticals, located in Aguas Buenas, PR. On July 10, 11, 14, and 18, 2003, FDA conducted an inspection of the firm and was accompanied at the end of the inspection by a representative from the Puerto Rico Health Department, Drugs and Pharmacy Division.

The Warning Letter advised that FDA was seriously concerned about the public health risk associated with the firm's large-scale production of massive quantities of inhalation solutions, without the same oversight provided by the laws and regulations applicable to a drug manufacturer. The need for this oversight was illustrated by the firm's recall of products distributed during the months of June and July 2003 because it did not have adequate testing procedures to determine satisfactory conformance to final specifications for identity and strength of each active ingredient.

The letter advised the firm that, while it purported to be a compounding pharmacy, FDA's investigation determined that the firm exceeded the scope of the regular course of the practice of pharmacy. The firm produced a significantly large number of batches of drug products that are essentially copies of commercially available products.

The Warning Letter also noted that the Puerto Rico Department of Health (PRHD) embargoed some of the firm's products because the pharmacy's operations were not in conformance with the applicable laws of Puerto Rico.

The firm was advised that the inhalation solutions made by the firm and defined as drugs within the meaning of Section 201(g) of the Act, are unapproved new drugs under section 505 of the Act, misbranded within the meaning of sections 502(f)(1) and 502(o) of the Act, and adulterated within the meaning of section 501(a)(2)(B) of the Act. The firm's drug products were also misbranded under Section 502(o) of the Act in that they were manufactured in an establishment not duly registered under Section 510 of the Act, and the articles were not listed as required by Section 510(j) of the Act. The facility is not exempt from the registration and drug listing requirements under Section 510(g) of the Act or 21 CFR § 207.10 in that the firm exceeds the scope of the regular course of the practice of pharmacy.

The firm was also advised that 21 CFR § 200.51 requires manufactured aqueous-based drug products for oral inhalation to be sterile, and, as set forth in 21 CFR § 201.57(a)(iv), the labeling of such products must indicate that they are sterile.

Warning Letters Issued for Compounded Injectable Products

Gentere, Inc., (d.b.a. Teregen)

On July 13, 2004, FDA's Cincinnati District Office issued a Warning Letter to George Fiderio, President of Gentere, Inc. (d/b/a Teregen Labs), located in Willoughby, Ohio. On August 19 and 21, 2003, and March 10-19, 2004, investigators from FDA and the Ohio State Board of Pharmacy inspected Gentere.

The inspection revealed that Gentere was producing and distributing large quantities of injectable drugs without valid prescriptions for individually identified patients from licensed practitioners, including drugs for general sale as "office stock" to physicians and clinics.

Many of the products that Gentere was producing were essentially copies of commercially available products. It appeared that the firm could not document a medical need for particular patients for these versions of otherwise commercially available products.

The Warning Letter advised Gentere that its drug products were unapproved new drugs in violation of section 505 of the Act. Because the firm was producing large volumes of drugs without valid prescriptions, and because many of these drugs were essentially copies of commercially available products, FDA will not exercise enforcement discretion with regard to this violation.

The firm was also advised that its drug products were misbranded under section 502(f)(1) of the Act because their labeling failed to bear adequate directions for use and they were not exempt from this requirement under 21 CFR § 201.115. The products were also misbranded under section 502(o) of the Act in that they were manufactured in an establishment not duly registered under section 510 of the Act, and the articles had not been listed as required by section 510(j) of the Act. Gentere is not exempt from registration and drug listing requirements under 21 CFR § 207.10 or section 510(g) of the Act.

Gentere's drug products were also adulterated under section 501(a)(2)(B) of the Act because the controls and procedures used in their manufacture, processing, packing, and holding do not conform to Current Good Manufacturing Practices regulations, 21 CFR Parts 210 and 211.

Delta Pharma

Size and Volume of Pharmacy "Compounding" Operation More Consistent with Drug Manufacturing Operation

On September 17, 2004, FDA's New Orleans District Office issued a Warning Letter to Tommy T. Simpson, M.D., President of Delta Pharma, located in Ripley, Mississippi. On March 8-10, 2004, investigators from FDA inspected Delta Pharma.

FDA's investigation determined that Delta Pharma's operation was consistent in size and production volume with a drug manufacturer. The firm was making large volumes of twelve injectable products. Many of these products were essentially copies of commercially available products without documented medical need for particular patients.

The firm's products were sold to physicians as "office stock," without requiring prescriptions for individual patients. The inspection noted that the firm used three wholesalers to obtain physician orders for Delta Pharma's products. Each wholesaler set their own price, invoiced customers, and received payment for the products shipped and then sends monthly payments to Delta Pharma. In at least one case, Delta Pharma shipped products on the wholesaler's behalf. These activities were not consistent with that of a pharmacy extemporaneously compounding drugs at retail.

The Warning Letter advised the firm that the volume of products that it manufactured, and the manner in which it dispensed those products, exceeded the scope of permissible pharmacy compounding. The letter further advised that FDA is seriously concerned about the public health risks associated with the large-scale production of injectable drugs by manufacturers that do not meet the laws and regulations applicable to drug manufacturing.

FDA advised that the products compounded by Delta Pharma were drugs within the meaning of section 201(g) of the Act. They were also new drugs, as defined by section 201(p) of the Act, because they were not generally recognized by qualified experts as safe and effective for their labeled uses, the products are new drugs. No approved application pursuant to section 505 of the Act is effective with respect to these products. Accordingly, their introduction or delivery for introduction into interstate commerce violates section 505(a) of the Act.

In addition, the Warning Letter noted that the firm's drug products were misbranded under section 502(f)(1) of the Act because their labeling failed to bear adequate directions for use and they were not exempt from this requirement under 21 CFR § 201.115.

The products were also misbranded under section 502(o) of the Act in that they were manufactured in an establishment not duly registered under section 510 of the Act and the articles had not been listed as required by section 510(i) of the Act. Delta Pharma is not exempt from registration and drug listing requirements under 21 CFR § 207.10 or section 510(g) of the Act.

The Warning Letter also advised that Delta Pharma's drug products were adulterated under Section 501(a)(2)(B) of the Act, because the controls and procedures used in the manufacture, processing, packing, and holding of the drug products did not conform to Current Good Manufacturing Practice Regulations, 21 CFR Parts 210 and 211.

Warning Letter Issued for Nicotine Lollipops

On January 16, 2004, FDA's Detroit District Office issued a Warning Letter to Ayed Shweihat, R.P.H., White Lake Pharmacy, White Lake, Michigan. The Warning Letter concerned Nicotine Lollipops, which were marketed by White Lake Pharmacy on the firm's Internet website www.whitelakecompounding.com. This product was being sold without a prescription. According to information on the Internet website, the product consisted of nicotine combined with a natural sweetener and flavorings in a sugar-free base, and available in 2 mg or 4 mg strengths. Nicotine Lollipops are intended as an aid for smoking cessation or to reduce nicotine addiction.

Nicotine Lollipops are smoking deterrent drug products and are subject to 21 CFR § 310.544. Under 21 CFR § 310.544, Nicotine Lollipops are considered "new drugs" by the Act and therefore may not be introduced or delivered for introduction into interstate commerce without an FDA approved application. Nicotine Lollipops were not the subject of an FDA approved application and therefore could not be marketed in

the U.S. The continued distribution of this product without an approved application violates the Act.

In addition, Nicotine Lollipops were misbranded in that they were manufactured in an establishment not duly registered under Section 510 of the Act and they had not been listed as required by Section 510(j) of the Act. Section 510(g) of the Act exempts from the registration and listing provisions pharmacies that dispense prescription drugs upon the prescription of a licensed practitioner. White Lake Pharmacy, by contrast, compounded and sold Nicotine Lollipops without requiring prescriptions and would not qualify for this exemption. Nicotine Lollipops may also be misbranded under Section 502(f)(1) of the Act on the grounds that their labeling failed to bear adequate directions for the uses for which they are being offered.

Postmarketing Adverse Drug Experience Reporting

Warning Letter Issued for Failure to Report ADEs

FDA Inspection Reveals Firm Had Never Filed ADE

On May 26, 2004, FDA's Atlanta District Office issued a Warning Letter to William S. Propst, Sr., President/CEO, Vintage Pharmaceuticals, Inc., Huntsville, Alabama. An FDA inspection of Vintage Pharmaceuticals, Inc.'s drug manufacturing facility in Charlotte, North Carolina, was conducted between March 29 - April 2, 2004. One of the purposes of that inspection was to determine the firm's compliance with the postmarketing Adverse Drug Experience (ADE) reporting requirements of Section 505(k) of the Act.

Section 505(k)(1) of the Act requires an applicant to establish and maintain records, and report data relating to clinical experience and other data or information for drugs for which an approval of an application filed under Section 505(j) of the Act is in effect. FDA's inspection revealed that Vintage Pharmaceuticals, Inc. violated Section 301(e) of the Act because it failed to comply with FDA's regulations.

FDA's inspection revealed significant deviations as follows:

- Failure to submit quarterly periodic ADE reports within 30 days of the close of the quarter. In fact, Vintage Pharmaceuticals, Inc. submitted no quarterly reports for any product covered by such an application;

- Failure to submit annual periodic Adverse Event Reports within 60 days of the anniversary date of the approval of the application. According to the firm's records this failure encompassed certain drug products listed under different abbreviated NDA numbers. Vintage Pharmaceuticals, Inc. submitted no annual reports for any product covered by such an application;

- Failure to develop adequate written procedures for the surveillance, receipt, evaluation, and reporting of PADE to FDA. Vintage Pharmaceuticals, Inc. established no procedures for the prompt review and identification of all ADE information obtained.

FDA's inspection revealed that Vintage Pharmaceuticals, Inc. had never submitted an ADE to FDA. This would include any 15 day alert, quarterly report or annual report for any application. The reports were being handled as all other incoming complaints.

Vintage Pharmaceuticals, Inc.'s complaint procedure did not address the identification and handling of ADE reports. A review of the complaint log by FDA investigators found several experiences which should have been reported under the ADE requirements. Although individuals at the firm were identified as being responsible for handling ADE reports, they had received no training in this area of the regulations.

Firm Fails to File 27 ADE Reports

On April 19, 2004, FDA's New Jersey District Office issued a Warning Letter to the President and CEO of Able Laboratories, Inc., South Plainfield, New Jersey. An FDA inspection of the firm from January 15 - February 4, 2004 was conducted to determine the firm's compliance with the ADE reporting requirements.

Based on FDA's review of the inspection report, the Agency concluded that Able Laboratories, Inc. violated the Act, because it failed to comply with 21 CFR 314.80 and Section 505(k)(1) of the Act. Section 505(k)(1) of the Act requires an applicant to establish and maintain records, and report data relating to clinical experience and other data or information for drugs for which an approved application is in effect.

Deviations from 21 CFR 314.80 observed during the inspection include the following:

- Failure to submit to FDA 27 ADE reports received by Able Laboratories, Inc. for drug applications owned by the firm;

  The 27 ADEs reported to Able Laboratories, Inc. between January 4, 2002 to January 16, 2004 were never reported to FDA. One of these complaints was by a patient taking Phentermine (Complaint C02C007).

The patient was taken to an emergency room for a possible "... left midbrain or pontine infarct."

- Failure to develop adequate written procedures for the surveillance, receipt, evaluation, and reporting of PADE to FDA;

  Able Laboratories, Inc. had not developed adequate written procedures for the surveillance, receipt, evaluation, and reporting of PADE to FDA.

The Warning Letter acknowledged receipt of both the 27 MedWatch reports Able Laboratories, Inc. submitted to the Agency, on or about February 20, 2004 and a copy of an SOP for the "Handling of Adverse Event Complaints," dated February 19, 2004. The Warning Letter noted that the MedWatch forms which Able Laboratories, Inc. submitted were on FDA Form 3500, which is for the voluntary reporting of ADEs by healthcare workers and consumers. As a drug manufacturer, Able Laboratories, Inc. must be reporting all domestic ADEs on FDA MedWatch Form 3500A.

FDA also provided the following comments regarding the revised SOPs which the firm submitted: "Able Laboratories, Inc. most recent submission dated February 19, 2004, references the reporting of ADEs under 21 CFR 314.80. This document however, makes references to SOP# CA-090, which still contains misinformation, such as the maintaining of ADE records for less then the required 10 years."

Prescription Drug Marketing Act

RxBazaar, Inc. and FPP Distribution, Inc. Plead Guilty

Firm Failed to Provide Drug "Pedigree" or "Statement Identifying Pharmaceutical Sale"

FDA announced on August 27, 2004, that two Cincinnati, Ohio area prescription drug wholesalers pleaded guilty in U.S. District Court for the Southern District of Ohio for failing to provide to their customers what is commonly referred to in the pharmaceutical industry as a drug "pedigree" or a "Statement Identifying Pharmaceutical Sale." This is one of the first convictions of its kind and marks a significant step in assuring that prescription drug wholesalers fully conform with laws that ensure the integrity of the nation's drug supply.

RxBazaar, Inc., and its wholly owned subsidiary, FPP Distribution, Inc., each pleaded guilty to 1 misdemeanor charge under the Act for not providing required documentation identifying each prior sale, purchase, or trade of prescription drugs that they distributed.

Each company was sentenced to 5 years probation and a $100,000 fine. RxBazaar, Inc., a publicly traded company, operated an Internet website www.rxbazaar.com through which buyers and sellers would conduct wholesale pharmaceutical transactions. RxBazaar, Inc. collected fees from sellers who utilized their Internet website and would distribute the pharmaceuticals to customers through FPP Distribution, Inc.

The Prescription Drug Marketing Act (PDMA), which became effective in 1988 as an amendment to the Act, was enacted amid growing concerns of prescription drug diversion and counterfeiting. One of the many provisions of PDMA is the requirement for drug wholesalers that are not manufacturers or authorized distributors of a drug to provide a pedigree for every prescription drug they distribute. Drug wholesalers that do not provide pedigrees, or provide fraudulent pedigrees, facilitate drug counterfeiters and diverters looking to enter illegal and potentially dangerous products into U.S. commerce.

Failure to comply with the pedigree requirement of PDMA, as well as other provisions of the Act, including the distribution of counterfeit drugs, are strict liability misdemeanors for which ignorance of the law or the lack of criminal intent is no defense. A second conviction for the same misdemeanor offense under the Act is a felony.

FDA's initiation of its criminal investigation followed several reports that drugs distributed by these companies were misbranded or counterfeit.

Promotional Claims/Labeling

Warning Letter Issued for Omission of Risk Information

Warning Letter Issued for Omission of Risk Information and Encouragement of Unsafe Use of Topamax In Pediatric Patients

On September 15, 2004, FDA's CDER, Division of Drug Marketing, Advertising, and Communications (DDMAC), issued a Warning Letter to Seth H.Z. Fischer, President, Ortho-McNeil Pharmaceutical, Inc., Raritan, New Jersey. The Warning Letter was issued regarding promotional materials and information regarding Topamax® (topiramate) Tablets, and Topamax® (topiramate capsules) Sprinkles Topamax® (topiramate).

The Warning Letter noted that DDMAC had reviewed a sales aid, two case study flashcards, and the Internet website www.topamax.com for Topamax® (topiramate) submitted by Ortho-McNeil Pharmaceutical, Inc. The Warning Letter advised the firm that the promotional materials omitted risk information about Topamax, in violation of the Act. In addition, the materials raised serious public health concerns, because they encouraged the unsafe use of Topamax, particularly, in pediatric patients.

The Warning Letter requested that Ortho-McNeil Pharmaceutical, Inc. immediately cease the dissemination of promotional materials for Topamax® the same as or similar to those described above. In addition, DDMAC requested that the firm submit a written response to the Warning Letter describing the firm's intent to comply with FDA's request, listing all promotional materials for Topamax® the same as or similar to those described above, and explaining a plan for discontinuing use of such materials. "Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, nonmisleading, and complete information to the audience(s) that received the violative promotional materials."

Warning Letter Issued for False or Misleading Claims

On September 2, 2004, FDA's CDER, DDMAC issued a Warning Letter to Ajit Shetty, M.D., CEO, Janssen Pharmaceutics, Inc. (Janssen), Titusville, New Jersey. The Warning Letter was issued regarding Duragesic® (fentanyl transdermal system) CII. DDMAC conducted a review of the professional file card for Duragesic® (fentanyl transdermal system) submitted by Janssen.

The Warning Letter advised Janssen that the file card made false or misleading claims about the abuse potential and other risks of the drug, and included unsubstantiated effectiveness claims for Duragesic. Thus, the file card misbrands the drug under Section 502(a) of the Act. The Warning Letter also noted that, by suggesting that Duragesic has a lower potential for abuse compared to other opioid products, the file card could encourage the unsafe use of the drug, potentially resulting in serious or life-threatening hypoventilation.

Unapproved Marketing

Warner-Lambert Pleads Guilty to Unlawful Marketing of Epilepsy Drug

U.S. v. Warner-Lambert. (D. Mass.). Warner-Lambert, a subsidiary of Pfizer Inc., agreed to plead guilty to 2 felony violations of the Act and to pay more than $430 million as part of a global settlement to resolve an investigation into the company's unlawful marketing of the epilepsy drug Neurontin. Pursuant to the settlement agreement, Warner-Lambert will pay a criminal fine of $240 million and approximately $190 million in civil damages.

Warner-Lambert Agrees to Pay $430 Million as Part of Global Settlement

Warner-Lambert pleaded guilty to 1 count of distributing an unapproved new drug in interstate commerce and 1 count of distributing a misbranded drug in interstate commerce. Both offenses are felonies because Warner-Lambert had a prior conviction for violating the Act. In addition, Pfizer Inc., Warner-Lambert's parent company, had entered into a corporate integrity agreement with the Department of Health and Human Services to ensure that Pfizer, Inc. provides adequate training and supervision to prevent future unlawful marketing of its drugs.

FDA approved Neurontin as an adjunctive treatment for adult epilepsy in December, 1993. Warner-Lambert marketed the drug for numerous unapproved uses, including bipolar disorder, neuropathic pain, attention deficit disorder, and migraines. Warner-Lambert's marketing scheme included the use of sales representatives and medical liaisons to promote Neurontin for unapproved uses to doctors without prior inquiry by the doctors. Warner-Lambert also paid doctors to attend expensive dinners or conferences during which information about the off-label uses of Neurontin was presented. In addition, Warner-Lambert sales representatives recruited doctors to participate in teleconferences to promote off-label uses of Neurontin. The conduct to which Warner-Lambert has agreed to plead guilty occurred prior to Pfizer, Inc.'s acquisition of Warner-Lambert in June 2000.